In the Claims:

Please rewrite the following claim:

137. (Twice amended) A polynucleotide comprising a nucleic acid fused in frame to a nucleotide sequence heterologous to SEQ ID NO:1, wherein said nucleic acid is selected from the group consisting of:

(a) a nucleic acid encoding amino acids 279 to 287 of SEQ ID NO:2;

(b) a nucleic acid encoding amino acids 292 to 300 of SEQ ID NO:2; and

(c) a nucleic acid encoding amino acids 317 to 325 of SEQ ID NO:2.

Remarks

Upon entry of the foregoing amendment, claims 24-39, 43-100, 105-139 and 141-155 will be pending in the application, with claims 24, 51, 75, 84, 105, 107, 109, 111, 121, 128, 137 and 149 being the independent claims. Claim 137 has been amended. This amendment introduces no new matter and entry thereof is respectfully requested.

Based on the above amendments and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Rejections under 35 U.S.C. § 112, first paragraph

The Examiner maintained the rejection of claims 137-148 under 35 U.S.C. 112, first paragraph, because allegedly "[t]he specification describes fusion polypeptides, whereas the claims are far broader since they do not restrict the 'nucleotide sequence heterologous to SEQ ID NO:1' to a nucleotide sequence [to one] that encodes an amino acid sequence in frame with a recited part of SEQ ID NO:2 to yield a fusion polypeptide as originally described." (Attachment to Paper No. 22 at page 2.)

Applicants respectfully disagree. One of ordinary skill in the art reading the claims in light of the specification would understand that "a nucleic acid fused to a nucleotide sequence heterologous to SEQ ID NO:1" would be particularly useful for generating a fusion polypeptide. However, for the sake of advancing prosecution, Applicants have amended claim 137 to recite "a nucleic acid fused in frame to a nucleotide sequence heterologous to SEQ ID NO:1." This amendment clarifies that a nucleic acid fused in frame to a nucleotide sequence heterologous to SEQ ID NO:1 will yield a fusion protein. Applicants note that the amendment to the claim does not narrow the claim in any way since Applicants intended to claim a fusion protein. Thus, withdrawal of this rejection is respectfully requested.

Claims 24-26, 28, 29, 31, 32, 34, 35, 37, 38, 40, 41, 43-53, 55, 56, 58, 59, 61, 62, 64, 65, 67-74, 105, 107, 109, 111 and 113-120 remained rejected under 35 U.S.C. § 112, first paragraph, because allegedly

> the proposed amendment does not overcome the rejection for the reasons of record regarding making polynucleotides encoding polypeptides to be used for making antibodies that the specification teaches how to use. Mere recitation of the function of antibody binding does not correct the deficiencies in the specification for <u>making</u> the embodiments without undue experimentation.

Attachment to Paper No. 22, at pages 2-3. Applicants respectfully disagree.

The specification of the captioned application provides a disclosure enabling one skilled in the art to make antibodies to a protein 90% identical to SEQ ID NO:2; thus, Applicants respectfully point out that the Examiner's statements regarding "undue experimentation" are incorrect. Undue experimentation is experimentation that would require a level of ingenuity beyond what is expected from one of ordinary skill in the field. *Fields v. Conover*, 443 F2d 1386, 1390-1391, 170 USPQ 276, 279 (CCPA 1971).

The factors that can be considered in determining whether an amount of experimentation is undue have been set forth in *In re Wands*, 858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Among these factors are: the amount of effort involved, the guidance provided by the specification, the presence of working examples, the amount of pertinent literature and the level of skill in the art. The test for undue experimentation is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine. *See id.*

In re Wands involved an appeal from the Board of Appeals and Patent Interferences, affirming the Examiner's rejection of immunoassay claims on the grounds that making anti-HBsAg antibodies for use in the claimed immunoassay, other than the deposited antibody, would be "unpredictable and unreliable, so that it would require undue experimentation for one skilled in the art to make the antibodies." *Id.* at 735, 8 USPQ2d at 1402. Antibodies other than the one deposited were described only in terms of function and only a general method of making and using them was disclosed in the application. *See id.* The facts showed that IgM antibodies were disfavored because they tended to self-aggregate and precipitate, isolating the correct antibodies required screening hundreds of clones, and the appellant's first four attempts were unsuccessful. *See id.* at 734, 8 USPQ2d at 1402. Nevertheless, the Federal Circuit found that the disclosure satisfied the requirements under

the first paragraph of 35 U.S.C. § 112. The court based its decision on the fact that the invention could be practiced with "readily available starting materials using methods that are well known in the monoclonal antibody art" and because "practitioners of the art are prepared to screen negative hybridomas in order to find one that makes the desired antibody." *See id.* at 736, 8 USPQ2d at 1406.

Applicants submit that the specification provides ample guidance for one skilled in the art to routinely make and use polynucleotides which encode polypeptides that can be used to raise antibodies which will bind to the native protein. For example, the specification discloses both the nucleic acid and amino acid sequences (SEQ ID NOs:1 and 2, respectively) of human PDEF and methods of making conservative substitutions. (*See, e.g.*, specification at page 17, lines 1-28.) Further, the specification teaches how to make phenotyically silent amino acid substitutions. (*See, e.g.*, pages 15-16.) The specification also teaches, *inter alia*, the preparation of monoclonal and polyclonal antibodies at pages 64-65 (Example 11). The specification, at pages 87-88 (Example 23), further teaches, *inter alia*, that monoclonal and polyclonal antibodies are useful for detecting PDEF gene expression in biological samples using antibody-sandwich ELISAs.

Applicants submit that the claims require that the claimed polynucleotides encode a polypeptide against which an antibody can be raised that binds a polypeptide consisting of amino acids 1 to 335 of SEQ ID NO:2. Thus, in order for the claimed polynucleotides to be capable of raising an antibody that binds a polypeptide consisting of amino acids 1 to 335 of SEQ ID NO:2, they should contain at least one, original, unmodified epitope. Contrary to the Examiner's assertion that "[the specification] provides limited guidance teaching specific epitopes that might be expected to be particularly antigenic," the specification describes at, *inter alia*, page 25, lines 10-16, that SEQ ID NO:2 was found

antigenic at certain amino acids using DNAstar analysis. For example, SEQ ID NO:2 was determined to be antigenic at amino acids Asp21-Glu29, Leu38-Ser46, Ser46-Gly54, Leu66-Ala74, Ala75-Arg83 and Glu84-Gln92. Thus, one of skill in the art would know which amino acid residues of the polypeptide could be substituted and still constitute a polypeptide which is capable of raising antibodies to PDEF. (*See., e.g.*, page 15, line 1, to page 16, line 11.) For example, one of ordinary skill in the art would know not to substitute amino acids within epitope-bearing regions in order to produce a polypeptide which is still useful for raising antibodies to these epitope-bearing portions of PDEF. Thus, one of skilled in the art could routinely determine which amino acids could be substituted while maintaining the epitope-bearing portions of PDEF.

According to the Examiner, "Applicant has provided no evidence that those skilled in the art routinely engage in the type of experimentation required to identify the operative embodiments embraced by the proposed claims; for example, intentionally altering the amino acid sequence for a natural protein in order to . . . make antibodies that recognize the natural protein." (Attachment to Paper No. 22, at page 3.)

The Examiner has, perhaps inadvertently, applied an improper standard. The legal issue is not whether those skilled in the art routinely engage in the type of experimentation required. Instead, the issue is whether it would require undue experimentation to practice the claimed subject matter. Indeed, in accordance with *In re Angstadt* and *In re Vaeck*, the relevant factual issue is not whether Applicants have provided evidence that those skilled in the art routinely engage in the type of experimentation required, but rather, whether the experimentation needed to *test* whether a polynucleotide is encompassed by the claims is undue, i.e., would require ingenuity beyond that to be expected from one skilled in the art.

First of all, the level of skill in the art of molecular biology is high. On the priority date of the instant application, several techniques were available for routinely generating polypeptides, using polynucleotides, and making modifications based on comparisons among homologs. Applicants submit that the skilled protein chemist or molecular biologist, enlightened by the teaching of the present specification, was more than capable of routinely determining which polynucleotide sequences fall within the scope of the claims.

Applicants submit that because of: (1) the availability of routine techniques for synthesizing polynucleotides and polypeptides; (2) the knowledge of the amino acid sequences of PDEF and homologs; (3) the high level of skill in the field of protein chemistry and molecular biology; and (4) the direction and guidance provided by the specification regarding polynucleotides and polypeptides with additions, substitutions, and/or deletions, one skilled in the art could routinely generate the claimed polynucleotides and determine whether the polypeptides encoded thereby could raise an antibody that binds a polypeptide consisting of amino acids 1 to 335 of SEQ ID NO:2. *This is especially true because antigenic epitopes of the PDEF protein are explicitly recited in the specification. Thus, as mentioned above, the specification provides specific guidance concerning which regions of the protein can be altered without affecting the ability of PDEF to bind an antibody.* Given the foregoing, it cannot be said that the invention as claimed is not fully enabled.

In view of the above comments, the captioned application enables one skilled in the art to practice the full scope of the claims. Applicants thus respectfully request that the Examiner reconsider and withdraw the outstanding rejection of the claims.

Allowable Subject Matter

The indication that claims 84-100 are allowed; claims 27, 30, 33, 36, 39, 54, 57, 60, 63, 66, 110 and 112 are allowable if rewritten in independent form; proposed claims 43, 67, 76, 113, 122 and 129 would overcome the rejection under 35 U.S.C. § 112, second paragraph; and proposed claim 75 would overcome the rejection of claims 75-83 under 35 U.S.C. § 112, first paragraph, is noted and appreciated by Applicants.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Preliminary Amendment and Reply is respectfully requested.

Respectfully submitted,

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